

Venetoclax for AML: changing the treatment paradigm

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Venetoclax is a specific B-cell lymphoma-2 (BCL-2) inhibitor that can restore activation of apoptosis in malignancies, the survival of which depends on dysregulation of this pathway. Preclinical data, using various model systems including cell lines and patient samples, suggested targeting BCL-2 could be a successful therapeutic strategy in patients with acute myeloid leukemia (AML). As predicted by this work, the use of venetoclax in the clinical setting has resulted in promising outcomes for patients with this disease. Although venetoclax showed limited activity as a single agent in the relapsed disease setting, recent studies have shown that when combined with a backbone therapy of a hypomethylating agent or low-dose cytarabine, high response rates with encouraging remission durations for older patients with newly diagnosed AML who were not candidates for intensive induction chemotherapy were observed. Furthermore, venetoclax-based therapies allowed for rapid responses and were able to effectively target the leukemia stem cell population. Here we review the preclinical data that supported the development of venetoclax in AML, as well as the results of the promising clinical trials.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in the adult population, and largely affects older patients, with a median age at diagnosis of 68 years.¹ The standard initial management for fitter patients with minimal comorbidities is intensive chemotherapy; older, less fit patients tolerate this poorly, resulting in limited effective treatment options. Historically, these patients have been referred for palliative or supportive care² or treated with single-agent hypomethylating agents (HMAs) or low-dose cytarabine (LDAC), which have modest response rates.³⁻⁵ The recent US Food and Drug Administration (FDA) approval of venetoclax with HMAs or LDAC in patients with AML who are previously untreated and older or unfit for chemotherapy has resulted in a promising therapy for these patients.^{6,7} Although the clinical development of this drug is still in its infancy, the preclinical efforts to deliver it to patients has been an ongoing effort for many years. Here we review the preclinical development of venetoclax and the results from relevant clinical trials and discuss how venetoclax may be used for patients with AML in the near future.

Preclinical development

The intrinsic apoptotic pathway

The B-cell lymphoma-2 (BCL-2) family includes multiple proteins sharing BCL-2-like homology domains 1-4 (BH1-BH4), each playing a specific role in the intrinsic apoptotic pathway. The BCL-2 family proteins' roles can be divided into 4 main functions: suppressors (BCL-2, BCL-XL, BCL-W, BCL2-A1, and MCL-1), activators (BIM and PUMA), effectors (BAX and BAK), and sensitizers (NOXA).^{8,9} Suppressors inhibit the activity of activators and effectors, preventing apoptosis, whereas sensitizers inhibit suppressors, releasing the brake on activators and effectors. The latter oligomerize, creating

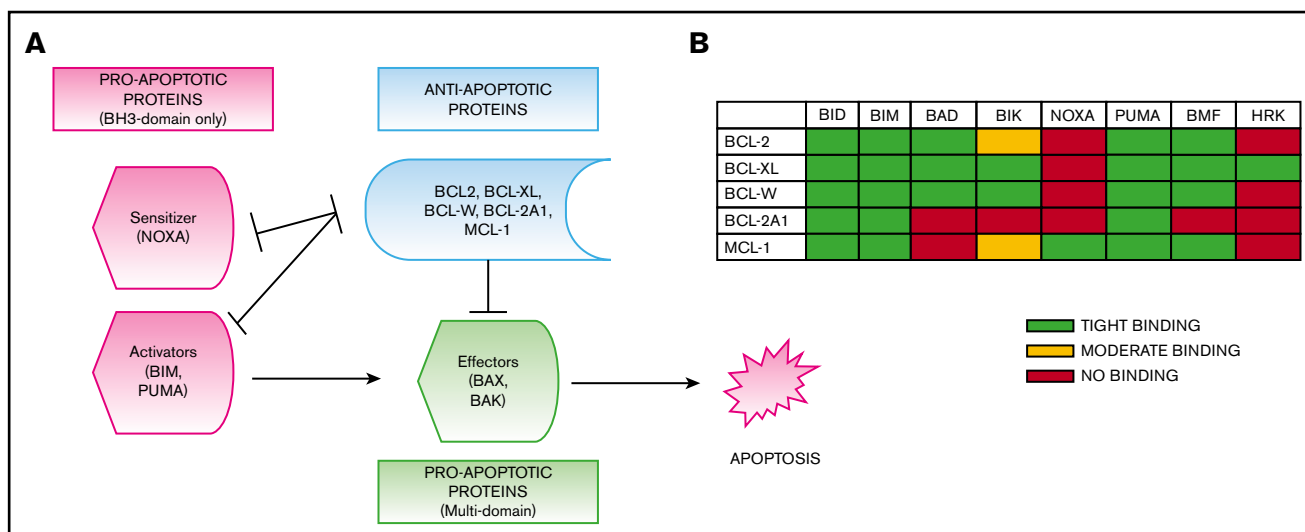


Figure 1. Intrinsic apoptosis pathway and BH3 profiling. (A) Proapoptotic mitochondrial proteins with BH3-domain only include NOXA (sensitizer), BIM, and PUMA (activators); proapoptotic mitochondrial proteins with multiple domains include BAX and BAK (effectors). Sensitizers and activators suppress (and are suppressed by) anti-apoptotic proteins, including BCL-2, BCL-XL, BCL-W, BCL2-A1, and MCL-1. Antiapoptotic proteins also suppress effectors. (B) BH3 profiling exploits the selective binding of BH3 peptides to specific antiapoptotic proteins (adapted from Certo et al).¹⁰

pores in the mitochondrial outer membrane, with subsequent release of cytochrome C and activation of caspase 9, ultimately leading to proteolytic cell death (Figure 1A).

One common property of malignancies is inappropriate cell survival and dysregulated apoptotic programs.¹¹ For this reason, since its identification more than 30 years ago,¹² it has been appealing to consider BCL-2 as a therapeutic target in cancer. Lymphoid malignancies provided the most obvious substrate for this strategy, given their near-universal overexpression of BCL-2,^{13,14} and this has proven to be successful, with FDA approval of the specific BCL-2 inhibitor venetoclax in chronic lymphocytic leukemia.^{15,16} BCL-2 was also an intriguing target in myeloid malignancies; unlike chronic lymphocytic leukemia, BCL-2 is not universally overexpressed in AML,^{17,18} but apoptosis is dysregulated in this disease.¹⁹

However, the mere expression of BCL-2 does not necessarily imply dependence, and any of the other suppressors can potentially drive leukemogenesis.⁸ In fact, although the 5 antiapoptotic proteins share homology in 1 or more BH domains, some proapoptotic proteins share homology only in the BH3 domain and have specific interactions with these 5 proteins (Figure 1B). As a consequence, by exposing mitochondria to known concentrations of BH3 peptides and measuring the resulting permeabilization of the outer mitochondrial membrane, it is possible to understand on what specific antiapoptotic proteins a cell is dependent for survival. This technique, called BH3 profiling, is considered the most accurate assessment of BCL-2 family members' dependence.^{10,20,21} Early studies confirmed AML cell lines not only express BCL-2 but also have a dependence on BCL-2 based on this assay.²²

Preclinical activity of single-agent venetoclax in AML

Initial attempts to synthesize inhibitors of these proteins failed because of technical limitations with protein-protein interaction targeting. This was overcome with the use of nuclear magnetic resonance-based screening, parallel synthesis, and structure-based design.²³ The first successful manipulation of

apoptosis for therapeutic gain came from the development of ABT-737, a BH3 mimetic with pleiotropic activity against BCL-2, BCL-XL, BCL-W, and to a lesser extent, MCL1.²³ Further development of these inhibitors led to ABT-263 (navitoclax), which was more orally bioavailable^{24,25} and was used in the clinical trial setting in patients with relapsed or refractory chronic lymphocytic leukemia.²⁶ However, navitoclax caused significant thrombocytopenia, limiting its enthusiasm for use in patients with AML.²⁷⁻²⁹ Another pan-BCL-2 inhibitor, GX15-070 (obatoclax), showed preclinical activity in AML cell lines, as well as primary samples, and was hoped to have more activity than ABT-737, given improved anti-MCL-1 activity, but had limited clinical efficacy in AML trials (see "Clinical development").^{30,31}

Venetoclax, formerly ABT-199, is a BH3 mimetic highly selective for BCL-2.³² Given the high degree of similarity of the BH3-binding domain of BCL-2 and BCL-XL, a unique BCL-2 small molecule co-crystal structure was used in the development of venetoclax to selectively target BCL-2. By not targeting BCL-XL, on which platelets precursors are highly dependent,^{24,31,33} venetoclax was engineered to circumvent significant thrombocytopenia, making it clinically viable for the treatment of AML, a disease typically associated with thrombocytopenia.³² In the first preclinical study in AML by Pan et al,³⁴ a similar sensitivity pattern was observed in AML cell lines in vitro with venetoclax and the dual BCL-2/XL inhibitor ABT-263. However, in BCL-2-sensitive cell lines (such as MOLM-13), more effective cell killing was observed with the use of venetoclax, likely as a consequence of its 5-fold higher affinity for BCL-2.³² These findings were confirmed in vivo, with an aggressive mouse xenograft model of MOLM-13, in which venetoclax resulted in significant inhibition of AML progression and extension of survival. Finally, ex vivo studies showed that both AML myeloblasts and AML stem/progenitor cells derived from patients' blood or bone marrow were highly sensitive to venetoclax, except for cases with complex karyotype and *JAK2* mutations. The limited efficacy of single-agent venetoclax in high-risk AML has encouraged the investigation of

Table 1. List of agents with preclinical evidence of synergy in combination with venetoclax in AML models

Drug name	Drug class
Chemotherapy	
Daunorubicin ³⁵	Anthracycline
Cytarabine ³⁵	Nucleoside analog
Epigenetic regulators	
Azacitidine ³⁶⁻³⁸	Hypomethylating agent
Panobinostat ³⁹	Histone deacetylase inhibitor
Targeted agents	
Alvocidib (flavopiridol) ⁴⁰	CDK9 inhibitor
MLN4924 (pevonedistat) ⁴¹	NED inhibitor
GDC-0980 ⁴²	PI3K/mTOR inhibitor
RG7388 (idasanutlin) ^{43,44}	MDM2 antagonist
GDC-0973 (cobimetinib) ⁴⁵	MEK inhibitor
A-1210477 ⁴⁶	MCL-1 inhibitor
VU661013 ⁴⁷	MCL-1 inhibitor
AMG 176 ⁴⁸	MCL-1 inhibitor
Quizartinib ⁴⁹	FLT3 inhibitor
Enasidenib ^{50,51}	IDH2 inhibitor

rationally designed combinations to increase its activity in these subgroups.

Combination strategies to boost venetoclax activity and overcome venetoclax resistance

BH3 profiling showed consistent positive correlation between venetoclax sensitivity and BCL-2 dependence, but negative correlation with MCL-1 dependence, encouraging the design of subsequent studies aimed at investigating combination strategies to boost venetoclax responses and overcome resistance (Table 1).³⁴

Niu et al investigated the activity of daunorubicin or cytarabine in combination with venetoclax, both in AML cells lines and patient-derived samples.³⁵ In vitro studies, conducted both in AML cell lines and patient-derived AML samples, the combination reduced MCL-1 protein levels (which was instead increased by the use of single-agent venetoclax), resulting in synergistic apoptosis of AML cells. Synergistic activity was subsequently reported for less intensive chemotherapy approaches as well, such as hypomethylating agents and histone deacetylase inhibitors. Tsao et al and Bogenberger et al demonstrated that the use of venetoclax sensitized both AML cell lines and patient-derived AML samples to the subsequent use of azacitidine.^{36,37} Of interest, although a more effective synergy was observed in vitro in AML cell lines with agents able to inhibit multiple members of the BCL-2 family, such as navitoclax, a similar potency was reported in primary AML and myelodysplastic syndrome/chronic myelomonocytic leukemia samples tested in ex vivo drug dose combination response assays when comparing the latter with venetoclax.^{37,38} This discrepancy was possibly because the AML-derived cell line panel had a greater dependency on BCL-XL and/or BCL-W than the primary samples analyzed ex vivo, as confirmed by BH3 profiling.³⁸ Schwartz et al reported synergistic induction of apoptosis with the combination of venetoclax and panobinostat, secondary to BIM upregulation, both

in AML cell lines and primary patient samples; in this study, shRNA knockdown of BIM in AML cell lines abrogated the benefit from the addition of panobinostat, highlighting the role of BIM as a potential mechanism to overcome MCL-1 mediated resistance to venetoclax in AML.³⁹

Multiple targeted agents, able to directly or indirectly affect MCL-1 function, have been investigated in combination with venetoclax in AML models. Bogenberger et al showed that alvocidib (also known as flavopiridol), a potent CDK9 inhibitor, downregulated MCL-1 expression and increased BIM expression, inducing synergistic apoptosis when combined with venetoclax in venetoclax-resistant AML cell lines (such as OCI-AML3), patient-derived samples, and a mouse xenograft model of OCI-AML3.⁴⁰ Knorr et al demonstrated that MLN4924 (also known as pevonedistat), an inhibitor of the Nedd8 activating enzyme, inactivated E3 cullin ring ligases, causing accumulation of the cullin ring ligase substrate c-Myc, which transactivated the PMAIP1 gene encoding NOXA, inducing upregulation of NOXA and subsequent MCL-1 inhibition. This led to synergistic apoptosis when combined with venetoclax both in cell lines and primary patient samples.⁴¹ Rahmani et al showed that GDC-0980, a PI3K/mTOR inhibitor, induced MCL-1 downregulation and BAX activation, resulting in marked apoptosis in resistant AML cell lines, patient-derived myeloblasts, and both in cell line-derived and patient-derived xenograft mouse models of venetoclax-resistant AML.⁴² Lehmann et al⁴³ and Pan et al⁴⁴ demonstrated that RG7388 (also known as idasanutlin), an MDM2 antagonist, activated p53, which negatively regulated the Ras/Raf/MEK/ERK pathway and activated GSK3 to modulate MCL-1 phosphorylation and promote its degradation; p53 additionally induced its downstream pro-apoptotic targets Bax and Noxa. This translated into synergistic induction of apoptosis when combined with venetoclax in p53-intact AML cell lines and xenograft mouse models of resistant AML.^{43,44} The efficacy and safety of the combination of venetoclax and idasanutlin has been investigated in a phase 1 study, including 39 patients with heavily pretreated relapsed refractory AML.⁵² Preliminary efficacy data have shown an overall response rate (ORR) of 46%, with mutations in *IDH1/2*, *RUNX1*, *JAK2*, *MPL*, and *CALR* associating with greater clinical benefit, and mutations in *FLT3* and/or *TP53* associating with primary and/or secondary refractoriness.⁵² By targeting the same pathway, Padua et al showed that GDC-0973 (also known as cobimetinib), a direct MEK inhibitor, was able to disrupt the RAS/BCL-2 complex in AML progenitors, overcoming resistance to venetoclax in patient-derived samples of AML.⁴⁵ Han et al subsequently demonstrated that this combination specifically targeted leukemia progenitors that express high levels of BCL-2 and causes the suppression of cytokine-induced pERK and pS6 signaling pathways exerted by cobimetinib. The combination downregulated MCL-1 and disrupted both BCL-2: BIM and MCL-1:BIM complexes, with the most marked effects being observed in cells lines enriched with pathways including MYC, mTORC1, and p53. This produced significant growth-inhibitory activity both in AML cells lines (including those resistant to single agents) and patient-derived samples (including those with multiple genetic aberrations), and translated into significant leukemia burden reduction in xenograft models using OCI-AML3 and MOLM13 cells.⁵³

Finally, multiple direct MCL-1 inhibitors have been investigated in combination with venetoclax in preclinical models of AML, including A-1210477, VU661013, and AMG 176. Luedtke et al investigated

the activity of A-1210477, alone or in combination with venetoclax, and observed synergistic induction of apoptosis both in AML cell lines and in patient-derived samples, secondary to decreased MCL-1 mediated sequestration of BIM.⁴⁶ Ramsey et al showed that VU661013 destabilized the association between BIM and MCL-1, leading to apoptosis in venetoclax-resistant AML cells and patient-derived xenografts, and showed significant activity in murine models of AML in combination with venetoclax.⁴⁷ Similar results were reported by Caenepeel et al, who showed that AMG176 was synergistic in combination with venetoclax in AML tumor models and in primary patient samples.⁴⁸

Clinical development

Targeting BCL-2 in the clinic: pre-venetoclax efforts

Before strategies to target BCL-2 with BH3 mimetics were employed, other approaches to inhibition of this protein were attempted. The antisense oligonucleotide oblimersen sodium was the most developed of these attempts. This agent showed some degree of activity in early clinical trials when used with induction chemotherapy,⁵⁴ but did not show a survival benefit in a phase 3 study with consolidation therapy in AML.⁵⁵ This result was perhaps a result of the long half-life of the BCL-2 protein,⁵⁶ which may have prevented sustained inhibition from an antisense oligonucleotide approach. The need for more potent inhibition of BCL-2 led to the development of BH3 mimetics (see "Preclinical development"). However, obatoclax, the BH3 mimetic and pan-BCL-2 inhibitor, showed minimal activity as a single agent in the untreated and relapsed AML settings.^{57,58} Efforts were thus made to develop a highly specific and potent BCL-2 inhibitor, which resulted in venetoclax, as summarized earlier.³²

Single-agent venetoclax in patients with relapsed and refractory AML

The first clinical trial of venetoclax in patients with AML was a phase 2 single-agent study in predominately relapsed and refractory patients. This study showed a modest ORR of 19%, with a median duration of remission of 48 days; another 19% of patients had antileukemic activity that did not meet criteria for response.⁵⁹ In this study, the most common adverse events (AEs) were nausea, diarrhea, hypokalemia, vomiting, and headache. The most common grade 3 or higher AEs were febrile neutropenia (31%), hypokalemia (22%), and pneumonia (19%), and there were no tumor lysis syndrome (TLS) events reported.

Venetoclax-based combinations in untreated patients with AML

After the results of the single-agent study, there was interest in assessing venetoclax in the frontline treatment setting and in combination with backbone therapies (HMAs and LDAC), given the synergistic activity seen in preclinical data.³⁶⁻³⁸ In addition, these backbone therapies were considered to be the standard of care for newly diagnosed elderly patients unfit for intensive chemotherapy, providing another, more practical, justification for combining them with venetoclax. In 1 study, an open-label dose escalation trial, previously untreated elderly patients who were ineligible for induction chemotherapy were treated with venetoclax and either azacitidine or decitabine at the standard dose and schedule.⁶ Eligible patients were aged 60 years or older who had not received

any prior therapy for AML, including HMAs. In addition, patients had to have adequate renal and hepatic function, an Eastern Cooperative Oncology Group performance status of 0 to 2, and a white blood count of 25×10^9 g/dL or less, although the use of hydroxyurea and/or leukapheresis were allowed to achieve this. The study had a dose escalation phase to determine the maximum tolerated dose of venetoclax plus HMA, followed by a dose-expansion phase assessing safety and clinical activity. During both phases, inpatient dose escalation of the venetoclax was performed during cycle 1, with close monitoring in the inpatient setting, to mitigate against the development of TLS. Bone marrow biopsies were performed at the time of screening, at the end of cycle 1, and at various prescribed points thereafter, depending on response status.

A total of 45 patients were enrolled in the dose escalation portion of the study; 22 received azacitidine and 23 received decitabine. There were 3 target doses of venetoclax (400, 800, and 1200 mg), and patients assigned to azacitidine and decitabine were enrolled into each of the 3 cohorts, for a total of 6 distinct groups of patients. Although in no cohort was the maximum tolerated dose reached, the 1200-mg dose had high frequency of gastrointestinal AEs (nausea in 82% and diarrhea in 64%). As a result, the 400- and 800-mg dose cohorts with both azacitidine and decitabine were expanded. In the original expansion, 25 patients were accrued to the 400- and 800-mg cohort of azacitidine and decitabine groups; an additional 55 patients were then added to the venetoclax 400-mg cohort with azacitidine, for a total of 80 patients in this cohort. In the intent-to-treat population (N = 145), the ORR was 83%; the complete remission (CR) rate was 37%, and the CR with incomplete recovery of blood counts (CRi) rate was 30%. At a median follow-up of 15.1 months, the median overall survival (OS) for all groups was 17.5 months (Figure 2). Specifically analyzing the 115 patients who received 400-mg venetoclax plus HMA revealed a CR/CRi rate of 71% for azacitidine and 74% for decitabine. The most common adverse effects were gastrointestinal events, and the most common grade 3 or higher AEs for all groups were thrombocytopenia (47%), febrile neutropenia (42%), and neutropenia (40%). No laboratory or clinical TLS was observed.^{6,60}

Jones et al have recently observed that leukemic stem cells (LSCs) in de novo AML rely on amino acid metabolism for oxidative phosphorylation and survival.⁶¹ Venetoclax with azacitidine was able to induce LSC toxicity in vitro by decreasing amino acid uptake, as confirmed by decreased α -ketoglutarate and increased succinate levels, suggestive of inhibition of electron transport chain complex II, observed in LSCs derived from patients with AML treated with this combination on a clinical trial.⁶² The potential to eliminate LSCs is further supported by the fact that among patients with AML not eligible for intensive chemotherapy who were treated with venetoclax in combination with azacitidine or decitabine, 45% of those achieving complete remission also experienced measurable residual disease eradication, with less than 10^{-3} leukemic cells observed in bone marrow samples at time of response assessment.⁶³ Measurable residual disease negative responses have also been reported, using more sensitive methods of detection.⁶⁴

Another study investigated venetoclax with LDAC.⁷ Similar to the HMA study described here, in this open-label, multicenter phase trial, previously untreated patients with AML who were aged 60 years or older and ineligible for induction chemotherapy were

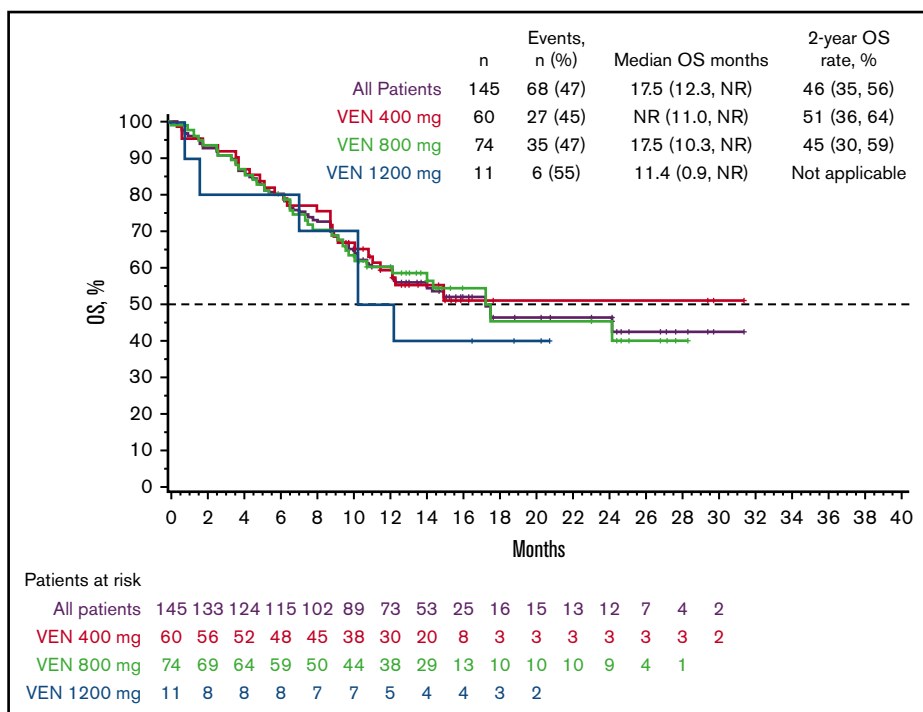


Figure 2. OS of elderly patients treated with venetoclax combined with decitabine or azacitidine. Kaplan-Meier curve showing OS survival of patients in the dose escalation as well as dose expansion phases of the trial.⁶⁰ OS is divided into the 3 different doses of venetoclax used in this trial. This figure was adapted from DiNardo et al.⁶⁰

treated with venetoclax and LDAC. The study eligibility was similar to the HMA study described here, with a major exception that patients who had been treated for a prior myelodysplastic syndrome with a HMA were eligible, whereas they were excluded from the HMA backbone study. Inpatient dose escalation and TLS mitigation techniques were employed in cycle 1; bone marrow biopsies were performed at a similar frequency as described for the HMA backbone study.

A total of 17 patients were enrolled in the dose escalation portion of the study. The maximum tolerated dose was not reached, and 600 mg daily was chosen as the expansion phase dose. Of the 82 patients who received 600 mg, the CR/CRi rate was 54% (CR, 26%; CRi, 28%). Thirty-three patients had had prior HMA exposure; the CR/CRi rate for this group was only 33%, whereas the group of patients who were treatment naive had a CR/CRi rate of 62%. The median OS was 10.1 months, and the median duration of response was 8.1 months. The most common AEs were nausea, diarrhea, and hypokalemia; the most common grade 3 or higher AEs were febrile neutropenia (42%), thrombocytopenia (38%), and neutropenia (27%). There were 2 cases of laboratory TLS and no reported clinical TLS.

The results of venetoclax in combination with HMA or LDAC seem to compare favorably with clinical trials that report outcomes from the backbone therapies as single agents in similar patient populations. Azacitidine was initially studied in a phase 3 clinical trial of patients with high-risk myelodysplastic syndrome; a subgroup analysis of patients with AML with 20% to 30% blasts from this study did not report the response rate, but reported a median OS of 24.5 months.⁶⁵ A follow up phase 3 trial of azacitidine in patients with AML with more than 30% blasts resulted in a CR rate of 19.5%, with an OS of 10.4 months.⁴ Decitabine showed a CR rate of 15.7% and OS of 7.7 months,⁵ and LDAC showed a CR of

2.3% and OS of 4.3 months.³ Attempts to compare results from independent and unrelated studies are fraught with bias, and should be interpreted with great caution; a randomized, placebo-controlled study comparing venetoclax with a backbone therapy and the backbone therapy alone will definitively measure any added benefit this drug provides. These studies, with azacitidine (NCT02993523) and LDAC (NCT03069352), are ongoing. Until those results are published, Table 2 summarizes clinical trial outcomes of single-agent HMA and venetoclax in combination with HMA or LDAC.

Another advantage of the addition of venetoclax to HMA backbones may be the rapidity of responses. With single-agent HMAs, median time to response was 4 cycles with azacitidine, and median time to achieve CR was 4.5 cycles with decitabine^{66,67}; median time to CR/CRi with the combination of venetoclax with azacitidine or decitabine was 1.2 months and 1 month, respectively.⁶

Because of the increased myelosuppression from the addition of venetoclax to a backbone therapy, blood count recovery may be slower or less complete with this regimen. The clinical consequences, in terms of progression-free survival or OS, and of CR vs CRi, are not yet fully understood. In addition, the relevance of other measures for count recovery, such as CRh, which increases the thresholds of count recovery to more clinically relevant levels than CRi, have also yet to be determined. However, mitigation of cytopenias with interruptions and dose reductions are increasingly being recognized as important features in the clinical use of these regimens.⁶⁸

Venetoclax-based therapies appear to have activity across the cytogenetic and genomic spectrum of this disease. Although prior HMA treatment and *TP53* mutations result in slightly lower response rates,^{7,60} most patients with traditional biologically defined adverse risks have overall high response rates, making this an appealing therapy for those whose disease features would

Table 2. Clinical trial outcomes using HMA, LDAC, BCL-2 inhibition or combination therapy

Regimen/trial	Population studied	FDA approval	Indication	ORR, %	CR, %	CRi, %	OS	Median duration of response
Oblimersen/Maruccucci et al ⁵⁵ (phase 3)	At diagnosis/in combination with consolidation	No	—	NR	48 (NS)	NR	36% 1 y (NS)	NR
Venetoclax/Konopleva et al ⁵⁹ (phase 2)	Relapsed or refractory	No	—	19	6	13	NR	155.6 d
Azacitidine/Dombret et al ⁴ (phase 3)	Newly diagnosed AML age ≥ 65 y, ineligible for SCT	No	— (used off-label for chemotherapy-ineligible patients)	27.8	19.5	8.3	46% at 1 y; median OS, 10.4 mo	10.4 mo
Decitabine/Kantarjian et al ⁵ (phase 3)	Newly diagnosed AML age ≥ 65 y;	No	— (used off-label for chemotherapy-ineligible patients)	25.6	15.7	9.9	Median OS, 7.7 mo (NS)	4.3 mo
Venetoclax 400 mg/azacitidine/Dinardo et al ⁶⁰ (phase 1b)	Newly diagnosed AML age ≥ 65 y, unfit for intensive chemotherapy	Yes	≥ 75 or those who are ineligible for induction chemotherapy because of comorbidities	76	44	27	Median OS, 16.9 mo	21.2 mo
Venetoclax 400 mg/decitabine/Dinardo et al ⁶⁰ (phase 1b)	Newly diagnosed AML age ≥ 65 y, unfit for intensive chemotherapy	Yes	≥ 75 or those who are ineligible for induction chemotherapy due to comorbidities	71	55	19	Median OS, 16.2 mo	15 mo
Venetoclax 600 mg/LDAC/Wei et al ⁷ (phase 1b/2)	Newly diagnosed AML age ≥ 65 y, unfit for intensive chemotherapy	Yes	≥ 75 or those who are ineligible for induction chemotherapy because of comorbidities	54	26	28	Median OS, 10.1 mo	8.1 mo

NR, not reported; NS, not significant.

predict a low likelihood of a good outcome from conventional therapies.

The overall toxicity profile of venetoclax with HMAs or LDAC includes hematological toxicities, with cytopenias occurring in about 40% of patients and grade 3 or higher infectious complications in 33% of patients.⁶ Despite these toxicities, only 3% of patients experienced early death,⁶⁰ reinforcing the safety of this regimen in this setting. On the basis of the above-described clinical data, in November 2018, the FDA granted accelerated approval for the combination of venetoclax with HMAs or LDAC for untreated patients with AML who were at least 75 years old or unfit for induction chemotherapy because of comorbidities.

Venetoclax resistance and novel venetoclax-based combinations

While we await the confirmatory phase 3 results, the high response rates reported for venetoclax-based combinations are exciting. However, up to a third of patients appear to be refractory, and this population does not have obvious traditional biological risk factors such as cytogenetic or molecular profiles, with the exception of *TP53* mutated patients, which may have lower response rates.⁶⁰ There are ongoing studies investigating the mechanisms of resistance of these patients, which include loss of BAX and inability of cells to undergo apoptosis,⁶⁹ and their dependency on CLBP, a chaperonin involved in maintaining mitochondrial cristae structure.⁷⁰ Targeting of these proteins resensitizes cells to venetoclax. Prior therapy with a HMA also appears to be a risk factor for refractory disease^{7,64} but more work is necessary to ascertain the biological mechanisms responsible for this nonresponsiveness to venetoclax. In addition, compared with patients treated at the time of diagnosis, patients with relapsed or refractory AML treated with venetoclax or venetoclax-based combinations have not achieved robust responses. In a study of 43 relapsed or refractory patients treated with venetoclax in combination with HMAs, LDAC, or other agents such as cladribine or midostaurin, the ORR was 21%.⁷¹ Finally, although the majority of newly diagnosed patients respond to venetoclax-based combinations, the median duration of response may only be around 1 year,⁶ necessitating an understanding of how resistance evolves, and how this can be targeted.

Novel venetoclax-based combinations and future directions

Multiple studies in recent years have directed their efforts toward investigating the efficacy of the combination of venetoclax with novel agents approved and clinically available for the treatment of patients with AML, such as FLT3 inhibitors and IDH1/2 inhibitors. Chyla et al have reported mutations in *FLT3* and/or *PTPN11* as possible mechanisms of intrinsic and acquired resistance to venetoclax, with 6 of 32 patients with relapsed or refractory AML carrying either of these mutations refractory to single-agent venetoclax in a phase 2 study and an additional 5 patients developing them at the time of relapse.⁴⁹ The same authors then investigated the efficacy of quizartinib, a FLT3 inhibitor, in combination with venetoclax in a FLT3-mutated xenograft mouse model and observed more durable responses with the use of both agents as compared with monotherapy. It is important to note that previous studies had shown that *FLT3-ITD* or *PTPN11* mutations could enhance the expression of other members of the BCL-2 family, including BCL-XL and MCL-1, providing a potential explanation for the resistance to venetoclax.^{72,73}

Chan et al performed a large-scale RNA interference screen to identify genes that were synthetic lethal to *IDH1/2* mutations in AML.⁷⁴ Interestingly, *IDH1/2*-mutant primary human AML cells were more sensitive to venetoclax than *IDH1/2* wild-type cells, both *ex vivo* and in xenograft mouse models. Similar findings were reported by Bordeleau et al, who conducted a chemical screen using a collection of about 300 drugs on a cohort of 38 primary human AML specimens, and observed an association between mutations in *IDH1/2* and sensitivity to venetoclax.⁷⁵ By producing R-2-hydroxyglutarate, *IDH1/2* mutant cells inhibit the activity of cytochrome c oxidase in the mitochondrial electron transport chain, lowering the mitochondrial threshold to trigger apoptosis on engagement with venetoclax. Supporting this preclinical finding, 4 of 6 patients with relapsed refractory AML who responded to single-agent venetoclax in a phase 2 study carried an *IDH1/2* mutation, and 12 of 16 patients with *IDH1/2* mutation had a decrease in bone marrow blasts.^{49,59} Furthermore, 18 of the 82 patients enrolled in the above-mentioned clinical trial investigating LDAC and venetoclax had *IDH1/2* mutations. The CR/CRi for this group was 72% compared with a CR/CRi rate of 54% in the overall study population.⁷ On the basis of these findings, the efficacy of enasidenib, an oral IDH2 inhibitor recently approved by the FDA for the treatment of patients with relapsed or refractory AML carrying an *IDH2* mutation, has been investigated in combination with venetoclax in 3 patient-derived xenograft models of human *IDH2*-mutant AML, showing a greater reduction in leukemia engraftment compared with single-agent therapy.^{50,51}

Because of the compelling preclinical evidence provided by the studies outlined here, several clinical trials have been initiated, investigating the activity of venetoclax in combination with FLT3-TKIs and IDH1 inhibitors for the treatment of patients with AML. These include phase 1/2 studies of the combination of venetoclax and the FLT3 inhibitors gilteritinib (NCT03625505) and quizartinib (NCT03735875) and a phase 1/2 study of the combination of venetoclax and the IDH1 inhibitor ivosidenib (NCT03471260). Several clinical trials investigating the combination of venetoclax and different chemotherapy regimens are also ongoing (NCT03709758, NCT03214562, NCT03586609).

Conclusions

Historically, the intensive nature of effective therapies for AML limited their use to younger, healthier patients, which is not the typical demographic of this disease; this left the majority of patients without reasonable treatment options. The approval of an effective and well-tolerated therapy such as venetoclax is therefore

a welcome addition to the AML armamentarium. However, this clinical advancement was not the result of serendipitous clinical investigations; the stage for the success of venetoclax was set many years before its approval in November 2018, with hypothesis-driven preclinical testing. Venetoclax in combination with HMAs and LDAC represents an exciting advancement for the AML field. The preclinical development occurred through a scientifically rigorous process and led to a well-tolerated and clinically active agent. Similar preclinical and clinical efforts are necessary, and underway, to improve on this regimen and continue to positively affect outcomes for patients with AML.

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